

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 50-731

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EA/FONSI				
Pharmacology Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 50-731

**Trade Name: DAUNORUBICIN HYDROCHLORIDE
INJECTION, 5MG/ML, 4ML VIALS**

Generic Name:

Sponsor: Bedford Laboratories

Approval Date: January 30, 1998

**INDICATION: Provides for the removal of the deficiencies
cited in the Approvable Letter dated November 31, 1998**

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA 50-731

APPROVAL LETTER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-731

APPROVABLE LETTER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-731

MEDICAL REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-731

CHEMISTRY REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-731

PHARMACOLOGY REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-731

MICROBIOLOGY REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-731

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-731

ADMINISTRATIVE DOCUMENTS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-731

CORRESPONDENCE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-731

JAN 30 1998

Bedford Laboratories
300 Northfield Road
Bedford, Ohio 44146

Attention: Robert V. Kasubick, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Kasubick:

Please refer to your new drug application dated July 29, 1997, received July 31, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Daunorubicin Hydrochloride Injection, 5mg/mL, 4 mL vials.

We acknowledge receipt of your submissions dated January 20 and 23, 1998. The User Fee goal date for this application is January 31, 1998.

This new drug application provides for the removal of the deficiencies cited in the Approvable Letter dated November 14, 1996.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 50-731. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Patrick Guinn, Project Manager, at (301) 827-1537.

Sincerely yours,

/s/

30 January 1998

Robert J. DeLap, M.D., Ph.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

cc:Original NDA 50-731

HFD-150/Div. files

HFD-150/CSO/P.Guinn

HFD-150/RDeLap

HFD-150/RJustice

HFD-150/DGriebel

HFD-150/JBeitz

HFD-150/JJee

HFD-150/RWood

HFD-150/WSchmidt

HFD-150/PAndrews

HFD-150/ARahman

HFD-150/MMehta

HFD-150/DPease

HFD-002/ORM (with labeling)

HFD-101/Office Director

HFD-810/ONDC Division Director

DISTRICT OFFICE

HF-2/Medwatch (with labeling)

HFD-92/DDM-DIAB (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613/OGD (with labeling)

HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.

HFD-560/OTC (with labeling - for OTC Drug Products Only)

HFI-20/Press Office (with labeling)

Drafted by: PGuinn/January 26, 1998

Initialed by: DPease/1-26-98

DGriebel/1-26-98

JBeitz/1-26-98

WSchmidt/1-27-98

PAndrews/1-27-98

ARahman/1-28-98

MMehta/1-28-98

JJee/1-27-98

RWood/1-27-98

JJee 1-29-98

RHWood 1-29-98 (as revised)

final: PGuinn/January 29, 1998

APPROVAL (AP)

AP
1-29-98



NDA 50-731

Bedford Laboratories
300 Northfield Road
Bedford, Ohio 44146

NOV 14 1996

Attention: Robert V. Kasubick, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Kasubick:

Please refer to your October 24, 1995 new drug application submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Daunorubicin hydrochloride.

We note that the due date for this application was delayed because the Administration did not receive the applicable user fee payment for this new drug application until November 20, 1995.

We acknowledge receipt of your amendments dated December 11, 1995, January 4, June 5, 18 and 21, August 5, and September 12, 1996.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit revised draft labeling and additional information in order to resolve the deficiencies listed below.

1. The deficiencies below pertain to Chemistry, Manufacturing and Controls (CMC).
 - a. The following comments pertain to the proposed regulatory specifications and methods for the drug substance, in-process controls, and drug product. This information should be provided in order for the Division to assess the adequacy of the analytical methods as written, and for the FDA Laboratories to validate the regulatory methods.
 - (1) The regulatory specifications and analytical methods for daunorubicin HCl drug substance on page 032 should be revised to include the following tests:

In addition, the regulatory specifications for daunorubicin HCl drug substance should contain the name and code number of the analytical method to be used for each determination.

- (2) On page 033, under _____ column, the designations _____ and their corresponding page citations cannot be found. Please explain these designations and the references cited.
- (3) What in-process testing is performed during the filling operation to assure content uniformity of the product?
- (4) For the drug substance, please provide the complete certificate of analysis for batch 920503 (PP 614 - 619) used by BVL as a secondary reference standard. In addition, please provide the tests and specifications used for residual solvents and impurities.
- (5) The regulatory specifications for the drug product, Daunorubicin HCl Injection (p. 559), should be revised to include the limits for identified and unidentified degradation products (individual and total). These specifications and the corresponding regulatory methods should be provided.
- (6) The current USP pH limits (4.5 to 6.5) for Daunorubicin HCl for Injection differ from the pH specifications _____ set for the finished dosage form (p. 559) and also differ from the pH specifications _____ set for the stability protocol (p. 627). Please provide an explanation for these differences.
- (7) For Daunorubicin HCl Injection, 5 mg/mL, the _____ specification in the BVL's Certificate of Analysis (p. 560) for Individual impurities is given as _____ %, and the sum of all impurities is not more than _____. These specifications differ from the regulatory specifications given on p. 559 and p. 627 and should be revised accordingly.

b. The following comments pertain to the drug product stability protocol.

- (1) Stability data have been submitted for only one lot (BVL Lot No. 768-43-0001) of the drug product at _____, inverted

and upright positions for three months (0, 1, 2, 3 months), and 2 °C to 8 °C, inverted and upright positions, for three months (0, and 3 months).

This lot is representative of % of the intended commercial batch size of vials. The stability data provided are insufficient to support the requested 24-month expiration dating period. Please refer to the FDA "Guideline for Industry: Stability Testing of New Drug Substance and Products" issued in September 1994.

- (2) The Bacterial Endotoxins test should be conducted at appropriate intervals (e.g., every 6 months) for Daunorubicin HCL Injection.
- c. The following pertains to the preparation of intravenous solutions:
- Please provide analytical methods, specifications, and test data to support the compatibility and stability of intravenous solutions of Daunorubicin HCl Injection with the recommended dilution solutions (5% dextrose or 0.9% sodium chloride), infusion system, concentration, and storage conditions. The protocol should include determinations of Daunorubicin HCl, decomposition products, pH, and particulate matter. We recommend using drug product samples that have been stored in their market containers for extended periods of time prior to dilution.
- d. The following comments pertain to the container/closure for the drug substance and drug product:
- (1) Please provide information on the container and storage conditions used for the bulk drug substance.
 - (2) authorization letter (p. 502) dated has authorized the agency to specifically refer to its Drug Master File (DMF)
The information given in the referenced DMF did not described the given on p. 500, pp 523 - 529, p. 562 and pp 633-636 (stability testing summary). Please submit an authorization letter for the proposed for use. In addition, please explain function (e.g., manufacturer, supplier, or testing laboratory).
 - (3) Please indicate who will perform the routine acceptance testing of the glass to meet the USP requirements. Please submit results of this testing.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Rockville MD 20857

NDA 50-731

JAN 30 1998

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Office of Drug Evaluation I
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ENCLOSURE

cc:Original NDA 50-731

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RWood/1-27-98

JJee 1-29-98

RHWood 1-29-98 (as revised)

final: PGuinn/January 29, 1998

APPROVAL (AP)

D. Andrews 1-29-98



NDA 50-731

Bedford Laboratories
300 Northfield Road
Bedford, Ohio 44146

NOV 14 1996

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 - (2) authorization letter (p. 502) dated has authorized the agency to specifically refer to its Drug Master File (DMF)
The information given in the referenced DMF did not described the given on p. 500, pp 523 - 529, p. 562 and pp 633-636 (stability testing summary). Please submit an authorization letter for the proposed for use. In addition, please explain function (e.g., manufacturer, supplier, or testing laboratory).
 - (3) Please indicate who will perform the routine acceptance testing of the glass to meet the USP requirements. Please submit results of this testing.

- (4) Please provide a certificate of analysis for the stoppers proposed for use and justify for the extraction solvent used for the USP recommended Tests for Elastomeric Closures for Injections. The extracting solvent should reflect the properties of the drug product formulation. A turbidity specification should be established.
 - (5) Please provide data on drug compatibility studies with the proposed closure system and validation information to show that the methods proposed can detect extractable components of the closure system without interference from daunorubicin and the excipients.
- 2. The following comment pertains to a microbiological issue which was included in your amendment dated June 5, 1996.

Please submit, post-approval, the data generated and conclusions for the product filtration bacterial retention study completed with product.
- 3. The following comments concern the Environmental Assessment.
 - a. Section 2 and 3 of the EA submitted on January 4, 1996 should be updated to reflect the change in ownership of the application.
 - b. Please state whether returned or expired goods will be disposed of in the same manner as described in the June 18, 1996 submission for "rejected drug product vials".
 - c. A certification of compliance with environmental requirements should be included for the drug substance manufacturer (see Industry Guidance, page 31, attached).
 - d. An MSDS for daunorubicin hydrochloride should be included in the EA.
 - e. The EIC calculation included in the June 18, 1996 submission is incorrect
 - f. The information provided on January 4, 1996, June 18, 1996 and in response to this letter must be released to the public in accordance with 40 CFR §1506.6. However, some of the information included appears to be confidential commercial information that could be excluded from release (e.g., marketing information). Please state that this information may be released or resubmit the information in an FOI releasable format. A discussion is provided in the Industry Guidance on what information can remain confidential.

4. In addition, it will be necessary for you to submit revised draft labeling identical in content to the enclosed marked-up draft labeling and with the revisions detailed below. Please note that these revisions may require you to review the current literature in order to update the labeling. The literature articles to support the labeling revisions should also be submitted for review.
- a. The phrase _____ should be used consistently throughout the labeling.
 - b. The DESCRIPTION section of the package insert should be revised to include the following changes:
 - (1) _____
 - (2) _____
 - c. The CLINICAL PHARMACOLOGY section of the package insert should be revised as follows:
 - (1) The suggested general format for this section is as follows:
 - (A) _____
 - (B) _____
 - (C) _____
 - (D) _____
 - (E) _____
 - (F) _____
 - (G) _____
 - (H) _____
 - (I) _____
 - (J) _____
 - (K) _____
 - (L) _____
 - (M) _____
 - (N) _____
 - (O) _____
 - (P) _____
 - (Q) _____
 - (R) _____
 - (S) _____
 - (T) _____
 - (U) _____
 - (V) _____
 - (W) _____
 - (X) _____
 - (Y) _____
 - (Z) _____
 - (2) The section currently entitled _____ should be made a subsection under this section.

- (3) The section currently entitled _____ should be divided into two subsections titled _____ and _____ Statements beginning with _____ and ending with _____ should be placed under a subsection entitled _____ The statements beginning with _____ and ending with _____ should be placed under a subsection entitled, _____
- (4) This section should also be updated based on the current literature. The pharmacokinetics of daunorubicin at the recommended dose and regimen administered in patients should be documented. Any information on effects of age, gender, ethnicity, renal and hepatic impairment on the pharmacokinetics of daunorubicin should be provided. Potential and possible drug-drug interactions should be mentioned.
- d. A CONTRAINDICATIONS section containing currently available information should be inserted following the INDICATIONS AND USAGE section.
- e. The _____ subsection of the WARNINGS section should be revised to include the following statements at the end of the second sentence:
- f. The PRECAUTIONS section should be revised as follows:
- (1) A new subsection entitled _____ should be created which contains paragraphs one, three, four, and five of this section.
- (2) The second paragraph in this section should be placed under a separate subsection entitled _____
- (3) The _____ subsection should be updated to reflect currently available information. There are several references in the literature concerning the mutagenic potential of daunorubicin in the Ames test, somatic cell mutation assay in *Drosophila*, sister chromatid exchange, etc.

- j. The following item should be included in the REFERENCES section:

- k. The following additional labeling comments should be considered.
- (1) The exact total volume of drug product solution (mL) per vial should appear on the proposed carton and vial labels.
 - (2) The word _____ should appear in all labeling.
 - (3) We suggest adding the statement _____ to all labeling.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of that FPL may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Dianne Spillman
Project Manager
Telephone: (301) 594-5770

Sincerely yours,



Robert J. DeLap, M.D., Ph.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES

cc:

Original NDA 50-731
HFD-150/Div. Files
HFD-2/M.Lumpkin
HFD-80
HFD-150/J.Beitz (with draft labeling)
HFD-150/R.Justice (with draft labeling)
HFD-150/J.Jee (with draft labeling)
HFD-150/R.Wood (with draft labeling)
HFD-150/W.Schmidt (with draft labeling)
HFD-150/J.DeGeorge (with draft labeling)
HFD-150/A.Rahman (HFD-860) (with draft labeling)
HFD-150/A.Lin (with draft labeling)
HFD-150/J.Johnson (with draft labeling)
HFD-150/D.Spillman/drafted:11-5-96 (with draft labeling)
HFD-101/L.Carter
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)

R/D Initialed by: J.Jee/11-7-96
R.Wood/11-8-96
W.Schmidt/11-8-96
M.Brower for J.DeGeorge/11-8-96
J.Beitz/11-8-96
R.Justice/11-12-96
D.Pease/11-7-96

F/T by: dds/11-12-96

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Handwritten: 11-12-96

APPROVABLE (AE)

OCT 29 1996

MEDICAL OFFICER REVIEW OF PRODUCT LABELING

NDA #50-731 Daunorubicin Hydrochloride Injection

Sept 12, 1996 (BL)

Sponsor: Bedford Laboratories

Information to be conveyed to the sponsor:

The following clinical comments on the proposed product labeling for daunorubicin hydrochloride should be conveyed to the sponsor:

The Section currently entitled _____ should be made a subsection
under the Section entitled, _____

The Section currently entitled _____ on page 3 should be divided
into two subsections. Statements beginning with _____
and ending with _____ should be
placed under a subsection entitled, _____
The statements beginning with
and ending with
should be placed under a subsection entitled,

A ' _____ Section should be inserted following the
Section containing currently available information.

In the ' _____ subsection of the _____ Section, the first sentence of the
second paragraph should be amended to:

In the _____ Section, a new subsection entitled _____ should be created
which contains paragraphs one, three, four and five. Paragraph two should be placed under a
separate subsection entitled,

The _____ subsection should be updated
using currently available information.

Section." should be amended to
Section.)

At the end of the _____ Section, insert the following subsections and provide
updated information under each:

Insert a seventh reference entitled, "OSHA Work Practice Guidelines for Personnel Dealing with
Cytotoxic (Antineoplastic) Drugs. *Am J Hosp Pharm* 43:1193-1204, 1986.

ISI

10/24/96

Julie Beitz, MD

Date

ISI

10/29/96

Robert Justice, MD

Date

cc:

NDA #50-731

HFD-150/ Division File

HFD-150/ J. Beitz

HFD-150/ W. Schmidt

HFD-860/ A. Rahman

HFD-150/ Dianne Spillman

HFD-150 / A. Lin

APR 16 1996

Daunorubicin NDA 50-731 1

MEDICAL OFFICER'S REVIEW OF NEW DRUG APPLICATION 50-731

PRODUCT: Daunorubicin Hydrochloride injection--5 mg/mL per vial

SPONSOR: Cetus-Ben Venue Therapeutics, Emeryville, CA 94608
Correspondance to be directed to Robert V. Kasubick, Ph. D.
300 Northfield Road, Bedford, OH 44146

INDICATION: Remission induction of adults and children with acute myelogenous leukemia, and of adults with acute lymphoblastic leukemia.

DATE SUBMITTED: Oct 25, 1995 **REVIEWED:** Dec 8, 1995

SUMMARY:

This application is for generic daunorubicin hydrochloride formulated as a sterile solution rather than the lyophilized powder as approved on December 19, 1979 for its innovator (currently Wyeth-Ayerst:). There are no alterations requested in indications. The label as presented is identical to that currently approved for the innovator drug, Cerubidine®, with the exception that the brand name is deleted and the formulation changed from powder to liquid.

In the Description section there is no mention that Daunorubicin is a topoisomerase II inhibitor, and in the Precautions section, under Carcinogenesis, Mutations, Impairment of Fertility, there is no mention of the induction of secondary acute myelogenous leukemia which has been reported for topoisomerase II inhibitors [1,2,3,4].

REGULATORY RECOMMENDATIONS:

- 1 Application is filable.
2. Application is approvable from a Medical Oncology standpoint if
 - a. the mechanism of action description is updated to include the Topoisomerase II inhibition, and
 - b. a warning regarding the risk of secondary leukemia following the use of Topoisomerase II inhibitors is added.the Precautions section.

The existing label for Cerubidine should be similarly changed.

- REFERENCES:**
1. Pui CH, Behm FG, Raimondi SC, et al. N Engl J Med 1989; 321:136
 2. Petersen-Bjersgaard J, et al. Lancet 1991; 338:359
 3. Whitlock JA, Greer JP, Lukens JH. Cancer 1991; 68:600
 4. Sandoval C, Pui CH, Bowman LC, et al. J Clin Oncol 1993, 11:1039

January 2, 1996

/s/

Edward S. Henderson, M.D.
Medical Officer, CDER Division of Oncology Drug Products

cc: HFD-150 files/NDA 50-731
HFD-150/JJohnson
HFD-150/RDeLap
HFD-150/EToglyesi
HFD-150/JJee
HFD-150/JDiGeorge
HFD-150/WSchmidt
HFD-150/DPease
HFD-150/DSpillman

January 2, 1996

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-731

CHEM. REVIEW # 2

REVIEW DATE: 1/21/98

SUBMISSION TYPE

ORIGINAL

Amendment

Amendment

DOCUMENT DATE

Oct. 24 95

July 29, 1997

January 20, 1998

CDER DATE

Oct. 25, 1995

July 31, 1997

Jan. 21, 1998

ASSIGNED DATE

Nov. 6, 1995

Aug. 12, 1997

Jan. 21, 1998

NAME & ADDRESS OF APPLICANT:

Bedford Laboratories TM

A Div. of Ben Venue Labs., Inc.

300 Northfield Rd.

Bedford, Ohio 44146

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/USAN:

Code Name/#:

Chem. Type/Ther. Class:

Daunorubicin Hydrochloride

Daunorubicin Hydrochloride

PHARMACOL. CATEGORY/INDICATION:

To be used in combination w/other approved anticancer drugs is indicated for the remission induction in acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) of adults and for remission induction in acute lymphocytic leukemia of children and adults.

DOSAGE FORM:

STRENGTHS:

ROUTE OF ADMINISTRATION:

DISPENSED:

Injectable

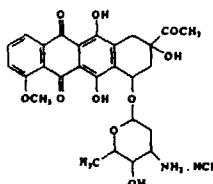
5 mg/mL, 4 mL vial

Intravenous

☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Daunorubicin Hydrochloride



$C_{27}H_{29}NO_{10} \cdot HCl$

MW: 563.99

5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)-, hydrochloride.

NDA 50-731 Review #2

RELATED DOCUMENTS (if applicable):**REMARKS/COMMENTS:**

Daunorubicin HCL for Injection USP, 20 mg base/vial approved on 2/3/95 and is currently marketed by BVL as a lyophilized cake, with the following formulation, per vial:

Daunorubicin Hydrochloride	Equivalent to 20 mg of daunorubicin
Mannitol	100 mg

The lyophilized product is reconstituted with 4 ml of Water for Injection, USP, to yield a solution containing 5 mg/ml of daunorubicin. The desired dose is then withdrawn into a syringe containing 10mL to 15 ml of normal saline and then injected into the tubing or sidearm of a rapidly flowing IV infusion of dextrose injection 5% or sodium chloride 0.9%.

CONCLUSIONS & RECOMMENDATIONS:

The amendment dated July 29, 1997 has addressed all the deficiencies listed on the Approvable letter dated 11/14/96. This application is approved from a CMC point of view.

cc:

Org. NDA 50-731

HFD-150/Division File

HFD-150/JJee/1/15/98

HFD-150/JJee/1/21/98

HFD-150/RWood

HFD-150/PGuinn

HFD-358/JCook

HFD-150/DPease

R/D Init by: RHWood 1-22-98

151

1/21/98

Josephine M. Jee, Review Chemist, DNDC I, HFD-150

filename: 50731r2a.wpd

CHEMISTRY REVIEW

Division of Oncology Drug Products

TYPE AND NUMBER OF APPLICATION : NDA 50-731 - Labeling Review 2
LABELING SUB. : 1/6/98 CDER DATE: 1/6/98 ASSIGNED DATE: 1/6/98

STATUS OF APPLICATION: Active

NAME OF SPONSOR: **Bedford Laboratories** (previous sponsor: Cetus Ben-Venue Therapeutics)

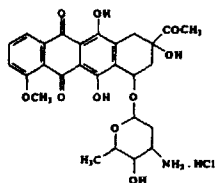
PRODUCT NAME: Daunorubicin Hydrochloride Injection

Proprietary: Same

Nonproprietary: Same

CHEMICAL STRUCTURE:

Daunorubicin Hydrochloride



$C_{27}H_{29}NO_{10} \cdot HCl$ MW: 563.99

DOSAGE FORM, STRENGTH, AND ROUTE OF ADMINISTRATION:
Injection, 5 mg/mL ; 4 mL/ vial, Infusion.

PROPOSED MARKETING STATUS: Rx

PHARMACOL. CATEGORY/ INDICATION:
Antimitotic and cytotoxic.

Package Insert:

Description section

The chemical name in the 1/6/98 e-mail is incomplete. Please refer to the BVL submission dated 7/29/97.

DOSAGE AND ADMINISTRATION

No necessary change.

HOW SUPPLIED

Adequate as per e-mail.

Vial Label

The word sterile should be added, see carton label.

ISI
1/7/98
Review Chemist, DNDC I, (HFD-150)

cc:
ORIG. NDA 50-731
HFD-150/Div. File
HFD-150/JJee/ 1/9/98
HFD-150/RWood
HFD-150/PGuinn
R/D Init. by: _____
Doc. #: 50731lab.2re

NOV 1 1996

CHEMISTRY REVIEW

Division of Oncology Drug Products

TYPE AND NUMBER OF APPLICATION : NDA 50-731 - Labeling Review
LABELING SUB. : 10/24/95 & 9/12/96 CDER DATE: 10-17-96 ASSIGNED DATE:
10/17/96

STATUS OF APPLICATION: Active

NAME OF SPONSOR: **Bedford Laboratories** (previous sponsor: Cetus Ben-Venue
Therapeutics)

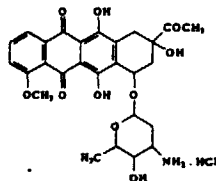
PRODUCT NAME: Daunorubicin Hydrochloride Injection

Proprietary: Same

Nonproprietary: Same

CHEMICAL STRUCTURE:

Daunorubicin Hydrochloride



$C_{27}H_{29}NO_{10} \cdot HCl$ MW: 563.99

DOSAGE FORM, STRENGTH, AND ROUTE OF ADMINISTRATION:

Injection, 5 mg/mL ; 4 mL/ vial, Infusion.

PROPOSED MARKETING STATUS: Rx

PHARMACOL. CATEGORY/ INDICATION:

Antimitotic and cytotoxic.

Package Insert:

Description section

1. Please add to sterile liquid in the second sentence.
2. Please add the equivalent amount of daunorubicin HCl in parenthesis after in the third sentence.
3. We recommend to name Daunorubicin HCl chemical name according to the USP 23.
4. The molecular formula should be written as $C_{27}H_{29}NO_{10} \cdot HCl$ as per USP 23.

NOTE: Daunorubicin hydrochloride should be consistently used throughout all sections of the labeling.

DOSAGE AND ADMINISTRATION

- a. Delete _____ in the first sentence.
- b. Change _____ to 0.9% Sodium Chloride Injection, USP.
- c. Change _____ to 5% Dextrose Injection, USP.
- d. A statement for storage condition and stability of the solution for infusion should be added.
- e. The statement _____ should be added.

HOW SUPPLIED

- a. The color, strength (5 mg/mL), total volume (4 mL) in a vial, and sterility of the drug product should be described in this section to facilitate identification of the drug product.
- b. Storage conditions and special handling and disposal should be added.
- c. Stability information (time and storage temperature) for unopened vials of Daunorubicin Injection and for prepared solution for infusion should be added.

In addition:

1. The exact total volume of drug product solution (_____ mL) per vial should appear on the proposed carton and vial labels.
2. The word _____ should appear in all labeling.
3. We suggest to add the _____ statement to all labeling.

/s/
10/31/96

Review/Chemist ~~/~~ ONDC I, (HFD-150)

cc:

ORIG. NDA 50-731

HFD-150/Div. File

HFD-150/JJee/ 10/31/96

HFD-150/RWood

HFD-150/DSpillman

R/D Init. by: _____

Doc. #: 50731lab.rev

RWood 10-1-96

OCT 16 1996
27

DIVISION OF ONCOLOGY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-731

CHEM. REVIEW # 1

REVIEW DATE: 10-03-96

SUBMISSION TYPE
ORIGINAL

DOCUMENT DATE
Oct. 24 95

CDER DATE ASSIGNED DATE
Oct. 25, 1995 Nov. 6, 1995

NAME & ADDRESS OF APPLICANT:

Cetus-Ben Venue Therapeutics
4560 Horton
Emeryville, California 94608

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/USAN:

Code Name/#:

Chem. Type/Ther. Class:

Daunorubicin Hydrochloride
Daunorubicin Hydrochloride

PHARMACOL. CATEGORY/INDICATION:

To be used in combination w/other approved anticancer drugs is indicated for the remission induction in acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) of adults and for remission induction in acute lymphocytic leukemia of children and adults.

DOSAGE FORM:

Injectable

STRENGTHS:

5 mg/mL, 4 mL vial

ROUTE OF ADMINISTRATION:

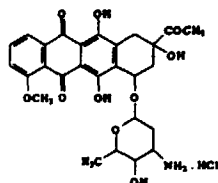
Intravenous

DISPENSED:

☒ Rx ☐ OTC

CHEMICAL NAME. STRUCTURAL FORMULA. MOLECULAR FORMULA. MOLECULAR WEIGHT:

Daunorubicin Hydrochloride



$C_{27}H_{29}NO_{10} \cdot HCl$

MW: 563.99

5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyranosyl)]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S-cis)-, hydrochloride.

SUPPORTING DOCUMENTS:**DMFs:**

DMF No.	Holder Name	Subject	Status	Date Reviewed	Reference in CR#1 review
		Daunorubicin HCL Drug Substance	Approved by OGD (M. Shih) on 5/11/94	5/11/94	
	Cetus-Ben Venue Therapeutics	Daunorubicin HCL for Injection USP, 20 mg base/vial	Approved by OGD(S. Rosencrance) on 2/3/95	2/3/95	
DMF			Satisfactory	4/25/96	
DMF			Reviewed by E. Duffy Satisfactory Re-reviewed by P. Dietze on 11/95 Satisfactory	6/9/93	

RELATED DOCUMENTS (if applicable):**CONSULTS:**

	<u>Consult Type</u>	<u>Status</u>	<u>Comments</u>
1.	Microbiology:	Rev.#1 by P. Stinavage, Ph.D. on 4/3/96. Rev. #2 by P. Stinavage, Ph.D. on 6/27/96	Consult sent on 11/28/95. See deficiencies. Approvable. Applicant should submit the data generated and concl. of the product filtration bacterial retention study completed w/ product.
2.	Env. Assess.	Pending	FONSI is being drafted by BVL. Spl. of FONSI was faxed on 7/1/96 to Shahid Ahmed. EA submitted on 10/17/95, 10/24/95, 12/11/95, & 1/4/96 were reviewed on 1/26/96 - Deficient. The applicant submission dated 6/18/96 & 6/21/96 responded to the deficiencies cited by

the review dated 1/26/96 - ok.

3. EER

Acceptable

Consult sent on 1/17/96

Satisf. by HFD-324 on 3/12/96

Note: On June 21, 1996, a letter from Bedford Laboratories was notifying the Agency about the change of ownership from Cetus Ben Venue Therapeutics to Bedford Labs. for the Daunorubicin HCL application. In addition, description of the manufacturing facility and the pertinent CADD drawings and the letter indicating change of ownership from Cetus Ben Venue to Bedford Labs. were included in this submission.

REMARKS/COMMENTS:

Daunorubicin HCL for Injection USP, 20 mg base/vial approved on 2/3/95 and is currently marketed by BVL as a lyophilized cake, with the following formulation, per vial:

Daunorubicin Hydrochloride	Equivalent to 20 mg of daunorubicin
Mannitol	100 mg

The lyophilized product is reconstituted with 4 ml of Water for Injection, USP, to yield a solution containing 5 mg/ml of daunorubicin. The desired dose is then withdrawn into a syringe containing 10mL to 15 ml of normal saline and then injected into the tubing or sidearm of a rapidly flowing IV infusion of dextrose injection 5% or sodium chloride 0.9%.

CONCLUSIONS & RECOMMENDATIONS:

The application is incomplete and some major questions remain. It can be considered Approvable from a CMC point of view only if the remaining deficiencies can be addressed satisfactorily.

cc:

Org. NDA 50-731

HFD-150/Division File

HFD-150/JJee/10-03-96

HFD-150/RWood

HFD-150/DSpillman

HFD-358/JCook

HFD-150/DPease

R/D Init by: RHWood 10-3-96

ISL

10/3/96

Josephine M. Jee, Review Chemist, DNDC I, HFD-150

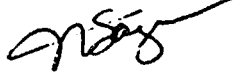
filename: 50731r1c.wpd

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 16, 1996

FROM: Nancy Sager, Team Leader, Environmental Assessment Team

SUBJECT: Review of EA and FONSI for NDA 50-731 

TO: Josephine Jee/Dianne Spillman/HFD-150

The review and unsigned FONSI are being returned to you with the following comments:

EA (submitted on January 4, 1996, amended June 18, 1996):

1. Section 2 and 3 of the EA submitted on January 4, 1996 should be updated to reflect the change in ownership of the application.
2. Please state whether returned and expired goods will be disposed of in the same manner as described in June 18, 1996 submission for "rejected drug product vials".
3. A certification of compliance with environmental requirements should be included for the drug substance manufacturer (see Industry Guidance, page 31, attached).
4. An MSDS for daunorubicin hydrochloride should be included in the EA.
5. The EIC calculation included in the June 18, 1996 submission is incorrect (need to divide by 365). The correct EIC is 3.4×10^{-8} ppm (0.03 pptr).
6. The information provided on January 4, 1996, June 18, 1996 and in response to this letter must be released to the public in accordance with 40 CFR § 1506.6. However some of the information included appears to be confidential commercial information that you could be excluded from release (e.g., marketing information). Please state that this information may be released or resubmit the information in an FOI releasable format. A discussion is provided in the Industry Guidance on what information can remain confidential.

The applicant can contact me directly if they have any questions.

FONSI

1. There are several changes needed. See the marked up copy that is attached. Other changes may be needed if the applicant classifies some information as confidential (e.g., EIC).

C.C

EA file 50-731

NDA 50-731

HFD-1SD/Dir Files

/R. Wood

/J. Jee

/D. Spillman

DIVISION OF ONCOLOGY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Review No.1 (original)

NDA No. 50731

Serial No(s): 000 Letter Date(s) of Submission: 10/25/95

Information to be Conveyed to Sponsor: Yes (), No (X)

Reviewer: Wendelyn J. Schmidt, Ph.D.

Date of Review: 11/29/95

Sponsor: Cetus/Ben Venue

Manufacturer (if different):

Drug Name: Primary: daunorubicin HCl Other Names:
Secondary:

Chemical Name: 7-(3-amino-2,3,6-trideoxy-L-lyxohexo-syloxy)-9-acetyl-7,8,9,10-tetrahydro-4-methoxy-5,12-naphthacenequinone hydrochloride

CAS Number:

Structure:

Molecular Weight (and Formula optional): $C_{27}H_{29}NO_{10}HCl$ mw=563.99

Referenced INDs/NDAs/DMFs: none

Related INDs/NDAs/DMFs: Wyeth-Ayerst NDA 50484 (approved 1979)

Class: anthracycline antineoplastic

Indication: remission induction in acute nonlymphocytic leukemia/myelogenous/monocytic/erythroid of adults and acute lymphocytic leukemia of adults/children

Clinical Formulation: reconstituted daunorubicin at 5 mg/ml, 4 ml/vial

Route of Administration: iv

Proposed Clinical Protocol: none

Previous Review(s), Date(s) and Reviewer(s):

Studies Reviewed for this submission: labeling

Studies Not Reviewed for this IND: none submitted

Studies Previously Reviewed for this IND:

Note: Portions of this review were excerpted directly from the sponsor's submission.

OVERALL SUMMARY AND EVALUATION

The sponsor is proposing to market a reconstituted form of daunorubicin (5 mg/ml, 4 ml/vial) of an already approved drug (NDA 50484, Wyeth Ayerst, approved 1979). No new studies (preclinical or clinical) were included with the submission. With a few minor exceptions (eg substituting "daunorubicin hydrochloride" for "cerubidine", and differences in the "Description" section), the wording is identical to the label for the Wyeth product.

RECOMMENDATION

The language in the submitted label matches that in the approved text for Wyeth cerubidine. The drug is approvable for Pharmacology.

a) Comments for further studies: none

NDA issues: none

Labeling Review: complete (see above)

To be marketed product issues (NDA only): Impurities, Extractables, and Excipients.

Draft Letter to the Sponsor:

File Name: Q N/I/PL/PM # /___/

151
11/29/95
Wendelyn J. Schmidt, Ph.D.
Pharmacologist/Toxicologist

c.c. Original IND/NDA/DMF
/Division File
/JDEGEORGE, Supervising Pharmacologist
/Medical Officer
/C.S.O.
/WSCHMIDT, Reviewer
/Pharmacology-Toxicology Assistant Director (NDA only)

010 — 12/21/95

Division of Oncology Drug Products, HFD-150

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Review No. 2

NDA No. 50-731

Serial No(s): Type: Label Date(s) of Submission: 10/25/95

Information to be Conveyed to Sponsor: Yes (X), No ()

Reviewer: Wendelyn J. Schmidt

Date Review Completed: 1/14/98

Sponsor: Bedford Laboratories/Ben Venue Manufacturer (if different):

Drug Name: Primary: Daunorubicin Hydrochloride Injection Other Names: daunomycin

Chemical Name: 7-(3-amino-2,3,6-trideoxy-L-lyxohexo-syloxy)-9-acetyl-7,8,9,10-tétrahydro-4-methoxy-5,12-naphthacenequinone hydrochloride

Molecular Weight (and Formula optional): $C_{27}H_{29}NO_{10} \cdot HCl$; MW= 563.99

Labeling Review

The following changes have been made to the label.

1) Clinical pharmacology

a) Mechanism of action (3rd paragraph): has been changed to

b) Distribution (2nd sentence): should be changed as follows:

c) The sentence has
been deleted and incorporated into the verbiage in the ' section.

The references are not meant to be incorporated into the official label, but are only to indicate the source of the information.

^a Weisberger, Cancer 40: 1935 (1977)

^b Solcia et al. Cancer Res. 38: 1444 (1978)

^c Thompson et al. Teratology 17:151 (1978)

/S/

Wendelyn J. Schmidt, Ph.D.
Pharmacologist/Toxicologist

1/26/98 (revision)
Date

Original IND/NDA/DMF

c.c. /Division File
/WSchmidt
/PAndrews
/DGriebel, Medical Officer
/PGuinn, Project manager

1/20/98

APR 3 1996

REVIEW FOR HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA 50-731
3 April 1996

A. 1. NDA 50-731

APPLICANT: Cetus - Ben Venue Therapeutics
4560 Horton
Emeryville, CA 94608

2. PRODUCT NAMES: Daunorubicin HCl Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is provided in 4 mL vials containing 5 mg/mL
for intravenous administration.

4. METHODS OF STERILIZATION:
The product is filled.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is indicated in combination with other approved
anticancer drugs and is indicated for remission induction
in acute nonlymphocytic leukemia (myelogenous, monocytic,
erythroid) of adults and for remission induction of acute
lymphocytic leukemia of children and adults.

B. 1. DATE OF INITIAL SUBMISSION: 24 October 1995

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: (none)

4. ASSIGNED FOR REVIEW: 12 December 1995

C. REMARKS: The drug product is compounded, filtered, filled,
sealed, labeled and packaged at Ben Venue
Laboratories, Inc., 300 Northfield Road, Bedford,
OH.

D. CONCLUSIONS: The application is approvable pending resolution
of microbiology issues.

Paul Stinavage, Ph.D.

3 April 1996

PKC 4/3/96

D. J. Williamson
JUN 27 1996

REVIEW FOR HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF NDA 50-731
26 June 1996

- A. 1. NDA 50-731
APPLICANT: Bedford Laboratories
300 Northfield Road
Bedford, OH 44146
2. PRODUCT NAMES: Daunorubicin HCl Injection
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is provided in 4 mL vials containing 5 mg/mL
for intravenous administration.
4. METHODS OF STERILIZATION:
The product is filled.
5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is indicated in combination with other approved
anticancer drugs and is indicated for remission induction
in acute nonlymphocytic leukemia (myelogenous, monocytic,
erythroid) of adults and for remission induction of acute
lymphocytic leukemia of children and adults.
- B. 1. DATE OF INITIAL SUBMISSION: 24 October 1995
2. DATE OF AMENDMENT: 5 June 1996 (Subject of this Review)
3. RELATED DOCUMENTS: (none)
4. ASSIGNED FOR REVIEW: 19 June 1996
- C. REMARKS: The drug product is compounded, filtered, filled,
sealed, labeled and packaged at Ben Venue
Laboratories, Inc., 300 Northfield Road, Bedford,
OH.
- D. CONCLUSIONS: The application is approvable, pending the
applicant's commitment to provide the data

ISI

26 June 1996

✓ Paul Stinavage, Ph.D.

JAC 6/26/96

JTe
FYZ

REVIEW FOR HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #3 OF NDA 50-731
12 November 1997

A. 1. NDA 50-731

APPLICANT: Bedford Laboratories
300 Northfield Road
Bedford, OH 44146

2. PRODUCT NAMES: Daunorubicin HCl Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is provided in 4 mL vials containing 5 mg/mL for intravenous administration.

4. METHODS OF STERILIZATION:
The product is filled.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is indicated in combination with other approved anticancer drugs and is indicated for remission induction in acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) of adults and for remission induction of acute lymphocytic leukemia of children and adults.

B. 1. DATE OF INITIAL SUBMISSION: 24 October 1995

2. DATE OF AMENDMENT: 29 July 1997 (Subject of this Review)

3. RELATED DOCUMENTS: (none)

4. ASSIGNED FOR REVIEW: 10 November 1997

C. REMARKS: The drug product is compounded, filtered, filled, sealed, labeled and packaged at Ben Venue Laboratories, Inc., 300 Northfield Road, Bedford, OH.

Bedford Labs, NDA 50-731; Daunorubicin HCl, Microbiologist's Review #3

D. CONCLUSIONS:

This submission fulfills the applicant's commitment to provide data specified in Microbiologist's Review #2.

/S/

Paul Stinavage, Ph.D. *12 November 1997*
JAC 11/20/97

cc: Original NDA 50-731
HFD-150/J. Jee/R. Wood/P. Guinn/D. Pease
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 12 November 1997
R/D initialed by P. Cooney

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

N 50,731

Submission Date: July 29, 1997

Drug Name, Dose, and Formulation: Daunorubicin Hydrochloride Injection, 20 mg vials

Sponsor: Bedford Laboratories
Bedford, Ohio 44146

Reviewer: N.A.M. Atiqur Rahman

Type of Submission: NDA Original Amendment

Category: 3S

BACKGROUND

In the submission, the sponsor has provided a revised "Clinical Pharmacology" section of the package insert according to the comments in the Agency's approvable letter dated November 14, 1996.

LABELING COMMENTS:

RECOMMENDATION

The package insert should be revised according to the comment provided in this review. Please convey the comment to the sponsor.

/S/

01/09/98

N.A.M. Atiquz Rahman, Ph.D.
Team Leader, Oncology
Division of Pharmaceutical Evaluation I

/S/

1/16/98

Mehul U. Mehta, Ph.D.
Deputy Director
Division of Pharmaceutical Evaluation I

cc: NDA 20-058 (orig),
HFD-150 Division File
HFD-150 D Griebel
HFD-850 LLesko
HFD-860 HMalinowski, MMehta, ARahman
CDR BMurphy

HFD-150 P Guinn
HFD-150 J Beitz

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Labeling Comments

NDA: 50-731 / *Sept 12, 1996 (BL)*

Drug, Dose, And Formulation: Daunorubicin hydrochloride injection, 5 mg/mL, 4 mL/vial

Sponsor: Bedford Laboratories

Reviewer: N.A.M. Atiqur Rahman

Submission: New Drug Application

The sponsor should update the Clinical Pharmacology section of the Package Insert based on the current literature. The pharmacokinetics of daunorubicin at the recommended dose and regimen administered in patients should be documented. Any information on effects of age, gender, ethnicity, renal and hepatic impairment on the pharmacokinetics of daunorubicin should be provided. Potential and possible drug-drug interactions should be mentioned.

Suggested general format for the Clinical Pharmacology section of the Package Insert is as follows:

The sponsor should submit the updated package insert along with the supported literature articles to the Agency for review.

/S/

N.A.M. Atiqur Rahman, Ph. D.
Team Leader, Oncology Drug Products
Division of Pharmaceutical Evaluation I

10/29/96

cc: NDA 50-731(orig)
HFD-150/Spillman
HFD-150/Division file
HFD-150/Medical Officer J. Bertz
A. Lin

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 50-731

Submission Date: October 24, 1995

Drug, Dose, And Formulation: Daunorubicin hydrochloride injection, 5 mg/mL, 4 mL/vial**Sponsor:** Cetus-Ben Venue Therapeutics
Emeryville, California 94608**Reviewer:** N.A.M. Atiqur Rahman**Submission:** New Drug Application**Background**

Daunorubicin hydrochloride is the hydrochloride salt of an anthracycline cytotoxic antibiotic produced by a strain of *Streptomyces coeruleorubidus*. Daunorubicin inhibits the synthesis of nucleic acid and displays an immunosuppressive effect. Daunorubicinol is the predominant active metabolite. The drug in combination with other approved anticancer drugs is indicated for remission induction in acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) of adults and for remission induction in acute lymphocytic leukemia of children and adults. Daunorubicin hydrochloride is currently marketed as a lyophilized cake, equivalent to 20 mg base, which upon reconstitution with appropriate amount of Sterile Water for Injection, provides a solution containing 5 mg/mL of daunorubicin. The proposed Daunorubicin Hydrochloride Injection, 5 mg/mL, 4 mL per vial, contains the same concentration of the active ingredient in a ready-to-use solution.

In accordance with Title 21 CFR 320.22, the sponsor is requesting a waiver of the requirement for submission of evidence demonstrating the in vivo bioavailability/bioequivalence for the drug product.

Proposed Changes

The currently approved drug product is a lyophilized cake which contains 100 mg mannitol. The lyophilized product is reconstituted with 4 mL of Water for Injection, USP, to yield a solution

containing 5 mg/mL of daunorubicin. The drug product submitted in this NDA is a ready-to-use solution which contains sodium chloride for isotonicity, hydrochloric acid or sodium hydroxide for pH adjustment, and water for injection. Upon reconstitution, the pH range for the currently marketed drug is , and the pH range for the new product is . The amount of the active ingredient (daunorubicin hydrochloride) is mg in both formulations.

Comments

1. The drug product being a homogeneous solution intended for immediate administration into an IV infusion, in accordance with 21 CFR 320.22 (b)(1) the sponsor is requesting a waiver of the requirement for an *in vivo* bioavailability/bioequivalency study for the NDA.

In § 320.22 (b) (1) (i) (ii) of the 21CFR the following is stated as criteria for waiver of evidence of *in vivo* bioavailability:

For certain drug products, the *in vivo* bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained *in vivo* bioavailability or bioequivalence of these drug products. A drug product's *in vivo* bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product :

- (i) Is a parenteral solution intended for administration by injection, or an ophthalmic or otic solution; and
- (ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application.

The submission does not fully meet the criteria set out in § 320.22 (b) (1) (i) (ii) in that the inactive ingredients are different in the two drug products . Although there is a change in the inactive ingredients, the replacement of with sodium chloride in the submitted drug product is not expected to alter the pharmacokinetics of daunorubicin hydrochloride following intravenous administration. Provided the Chemistry Reviewer is satisfied with the stability and general quality assurance of the product, the Division of Pharmaceutical Evaluation I waives the requirement for evidence of *in vivo* bioequivalence.

Recommendation

The Division of Pharmaceutical Evaluation I has reviewed the formulation and waiver request submitted in this NDA. The submission does not fully meet the criteria set out in § 320.22 (b) (1) (i) (ii); however, the drug product will be administered intravenously, and the pharmacokinetics of the active ingredient should be unaltered by the formulation change. Provided the Chemistry Reviewer is satisfied with the stability and general quality assurance of the product, the Division of Pharmaceutical Evaluation I waives the requirement for evidence of *in vivo* bioequivalence. The Reviewing Medical Officer needs to concur with this recommendation.

/s/

N.A.M. Atiqur Rahman, Ph. D. 02/29/96
Team Leader, Oncology Drug Products
Division of Pharmaceutical Evaluation I

/s/

 2/29/96
Mehul U. Mehta, Ph.D.
Deputy Director
Division of Pharmaceutical Evaluation I

cc: NDA 50-731
HFD-150/Spillman
HFD-150/Division file
HFD-150/Medical Officer /Henderson
HFD-850/LLesko
HFD-860 (Malinowski, Mehta, Rahman)
HFD-850 (Drug, Chron, Reviewer's files)
HFD-340/ Viswanathan
HFD-205/FOI

CETUS-BEN VENUE THERAPEUTICS

Daunorubicin Hydrochloride Injection - 5 mg/mL, 4 mL per vial

Section VI Bioavailability/Bioequivalency

Request for Waiver of In Vivo Studies [314.94(a)(7)]

A waiver of the requirement for an IN VIVO bioavailability/bioequivalency study is requested for the drug products that are the subject of this application (Daunorubicin Hydrochloride Injection - 5 mg/mL, 4 mL per vial) in accordance with 21 CFR 320.22 (b)(1). The drug product is a homogeneous solution, intended for immediate administration into an IV infusion.

CSO LABELING REVIEW

NDA #: 50-731

SUBMISSION DATES: October 24, 1995 & September 12, 1996

PRODUCT: Daunorubicin Hydrochloride Injection, 5 mg/mL; 4 mL/vial

SPONSOR: Bedford Laboratories (previous sponsor: Cetus-Ben Venue Therapeutics)

DATE REVIEW COMPLETED: October 17, 1996

BACKGROUND: The sponsor for this New Drug Application (NDA) is proposing to market a ready-to-use formulation of an approved drug product, Cerubidine (daunorubicin hydrochloride) for Injection. Thus, the labeling for this pending application was compared to the latest approved labeling for Wyeth-Ayerst's Cerubidine, NDA 50-484 / SLR-005.

The labeling from both the October 24, 1995 and September 12, 1996 submissions are reviewed here. Note that comments in *italics* pertain to the September 12, 1996 submission. These changes were either editorial changes effected by the NDA sponsor or changes recommended by the previous medical officer/team leader.

REVIEW:

1. The words has been
substituted for the proprietary name,
throughout the labeling.
2. **DESCRIPTION** section.
 - a. The following phrase in the second sentence was changed
from:
to:
 - b. The third sentence was changed
from:
to:
 - c. The fourth sentence has been deleted:

d. In the fifth sentence, the hyphen between the phrases has been deleted.

e. In the sixth sentence, the phrase has been replaced with

► **CSO NOTE:** Should the sentence: be deleted?

f. The last sentence was changed

from:

to:

g. The structural formulas are different.

3. **ACTION** section.

a. The section title has been omitted.

*However, the September 12, 1996 labeling lists the section title as **MECHANISM OF ACTION**.*

► **CSO NOTE:** 21 CFR §201.56(d)(1) does not provide for an **ACTION** or **MECHANISM OF ACTION** section; however, review of other product labeling presented this information as a subsection under the **CLINICAL PHARMACOLOGY** section.

b. *In response to a request posed by the previous medical officer, Edward Henderson, M.D., the following paragraph has been added after the first paragraph:*

► **CSO NOTE:** There is no **CONTRAINDICATIONS** section.

4. **WARNINGS** section.

In the **Cardiac Effects** subsection, the first sentence of the second paragraph was changed from:

to:

9-12-96 labeling. Above error still there.

5. **PRECAUTIONS** section.

In response to a request posed by the previous medical officer, Edward Henderson, M.D., the following paragraph has been added after the second paragraph:

- ▶ **CSO NOTE:** This section should be formatted to include a **General** and **Pediatric Use** subsection to comply with 21 CFR §201.57(f).

6. **DOSAGE AND ADMINISTRATION** section.

- ▶ **CSO NOTE:** *The 9-12-96 labeling: In the first sentence of the fifth paragraph, the superscript should be deleted*

a. In the tenth paragraph:

(i) The following sentence in the has been deleted:

(ii) The following phrase was changed in the third sentence:

from:

to:

(iii) The following has been deleted:

and replaced by:

- c. In the last paragraph, the reference numbers, provided as superscripts, which pertain to handling and disposal guidelines have been changed from because the order of the references were re-arranged.

*However in response to the Division's request, the **REFERENCES** section has been revised and all references have been deleted except for those that referred to safe handling, and as such the reference numbers have been changed from*

7. **HOW SUPPLIED** section.

This whole section was changed

from:

to:

8. **REFERENCES** section.

*In response to the Division's request, the **REFERENCES** section has been revised and all references have been deleted except for those that refer to safe handling.*

- **CSO NOTE:** *A review of other product labeling revealed that a reference pertaining to handling of chemotherapeutic agents has been omitted, specifically the OSHA Work-Practice guidelines.*

/S/

10/17/96

Dianne D. Spillman /date
Consumer Safety Officer

cc: NDA 50-731
HFD-150/Div. File
/JBeitz
/JJee
/RWood
/WSchmidt
/JDeGeorge
/ARahman
HFD-151/DDSpillman

*2-1-96
11-6-96*

AUG 27 1996

NDA 50-731

Bedford Laboratories
300 Northfield Road
Bedford, Ohio 44146

Attention: Robert V. Kasubick, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Kasubick:

We acknowledge receipt of your correspondence responding to the Food and Drug Administration's August 7, 1996 request regarding the change of ownership of the following new drug application (NDA):

Name of Drug: Daunorubicin Hydrochloride Injection - 5 mg/mL, 4 mL vial

NDA Number: 50-731

Date of Submission: August 13, 1996

Date of Receipt: August 15, 1996

Name of New Owner: Bedford Laboratories

Name of Previous Owner: Cetus-Ben Venue Therapeutics

Your correspondence provided the information necessary to effect this change and we have revised our records to indicate Bedford Laboratories as the sponsor of record for this application.

Should you have any questions, please contact:

Dianne Spillman
Project Manager
Telephone: (301) 594-5770

Sincerely yours,

/s/

8-26-96

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Office of Review Management
Center for Drug Evaluation and Research

NDA 50-731
Page 2

cc:

Original NDA 50-731

HFD-150/Div. Files

HFD-80

HFD-150/CSO/D.Spillman/draft: 8-21-96

HFD-150/Jee

DISTRICT OFFICE

R/D init. by: D.Pease\8-21-96

F/T by: dds/8-26-96

a:\50731dau.bed\admin\ltrs\xs-ltr#2

ACKNOWLEDGEMENT of CHANGE OF OWNER (AC)

11
D. Spillman

NDA 50-731

AUG - 7 1996

Bedford Laboratories
Division of Ben Venue Laboratories, Inc.
300 Northfield Road
Bedford, Ohio 44146

Attention: Robert V. Kasubick, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Kasubick:

We acknowledge receipt of your correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug: Daunorubicin Hydrochloride Injection - 5 mg/mL, 4 mL vial

NDA Number: 50-731

Date of Submission: June 20, 1996

Date of Receipt: July 3, 1996

Name of New Owner: Bedford Laboratories

Name of Previous Owner: Cetus-Ben Venue Therapeutics

Your correspondence provided most of the information necessary to effect this change; however, under 21 CFR 314.72, the following information is required to complete the change of ownership procedure:

1. A new Form FDA 356h signed by an authorized agent or official of the company.

Should you have any questions, please contact:

Dianne Spillman
Project Manager
Telephone: (301) 594-5770

Sincerely yours,

8-6-96

/S/

8-6-96

Dotti Pease
Chief, Project Management Staff
Division of Oncologic Drug Products
Office of Drug Evaluation I
Office of Review Management
Center for Drug Evaluation and Research

cc:

Original NDA 50-731
HFD-150/Div. Files
HFD-84
HFD-150/D.Spillman/draft: 7-15-96
DISTRICT OFFICE

R/D init. by: DPease/7-16-96
F/T by: dds/8-5-96
a:\50731dau.bed\admin\ltrs\xs-ltr

INFORMATION REQUEST (IR)

D. Spillman

NDA 50-731

Cetus-Ben Venue Therapeutics
4560 Horton
Emeryville, California 94608

NOV 27 1995

Attention: Robert V. Kasubick, Ph.D.,
Vice President, Regulatory Affairs

Dear Dr. Kasubick:

We have received your new drug application submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Daunorubicin Hydrochloride Injection

Therapeutic Classification: Standard

Date of Application: October 24, 1995

Date of Receipt: November 20, 1995

Our Reference Number: 50-731

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 507 of the Act on January 19, 1996 in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact:

Dianne Spillman
Oncology Drugs Project Manager
Telephone: (301) 594-5770

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/s/

11-21-95

Dotti Pease
Chief, Project Management Staff
Division of Oncologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA 50-731

Page 2

cc:

Original NDA 50-731

HFD-150/Div. Files

HFD-80

HFD-150/DDSpillman/11-20-95

R/D init by: DPease/11-21-95

F/T: dds/11-21-95

a:\50731dau.cbv\un-ar-ac.ltr

UNACCEPTABLE for FILING (UN)

and

ACKNOWLEDGEMENT of RECEIPT of PAYMENT (AR)

OCTOBER 24 1995
Original NDA Submittal

CETUS-BEN VENUE THERAPEUTICS

Daunorubicin Hydrochloride Injection - 5 mg/mL, 4 mL per vial

Section III Patent Certification

This section is not applicable to this application, as this is a New Drug Application, pursuant to Section 505 (b)(2) of the Federal Food, Drug and Cosmeti Act.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 50-731 Supplement # - Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-~~150~~ Trade (generic) name/dosage form: Doxorubicin hydrochloride Action: AP AE NA
Injection

Applicant Bedford Laboratories Therapeutic Class _____

Indication(s) previously approved _____ Pediatric labeling of approved

indication(s) is adequate _____ inadequate _____

Indication in this application REMISSION INDUCTION IN (1) ADULT ACUTE NONLYMPHOCYTIC LEUKEMIA + (2) ACUTE LYMPHOCYTIC LEUKEMIA OF CHILDREN + ADULTS (For supplements, answer the following questions in relation to the proposed indication.)

☐ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

☐ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

☐ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

☐ b. The applicant has committed to doing such studies as will be required.

☐ (1) Studies are ongoing,

☐ (2) Protocols were submitted and approved.

☐ (3) Protocols were submitted and are under review.

☐ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

☐ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

☐ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

☒ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form. (OVER →)

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

JSI

CSO

November 13, 1996

Signature of Preparer and Title (PM, CSO, MO, other)

Date

cc: Orig NDA/PLA # 50-731

HFD-150 /Div File

NDA/PLA Action Package

HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

HFD-150/CSO/DO Spillman

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

APPROVABLE LETTER REQUESTS SPONSOR TO REVIEW CURRENT LITERATURE
AND UPDATE THE LABELING WITH INFORMATION ON PEDIATRIC USE, WITH
EMPHASIS ON SAFETY / EFFICACY IN NEONATES.

Cetus-Ben Venue Therapeutics

4560 Horton
Emeryville, California 94608
(510) 420-3300

CERTIFICATION OF PERSONNEL

This is to certify that Cetus-Ben Venue Therapeutics did not and will not use, in any capacity, the services of any individual debarred by the United States Food and Drug Administration, under Section 306 (a) or (b), in connection with this application.

RELEVANT CONVICTIONS

Further, we certify that Cetus-Ben Venue Therapeutics, and all persons affiliated with this application have no relevant convictions, subject to debarment, to submit, in accordance with Section 306 (a) or (b).

for Cetus-Ben Venue Therapeutics

Thomas Russillo 10/17/95

Thomas Russillo
President, Ben Venue Laboratories, Inc.

NDA # 50-731

Drug: Daunorubicin Hydrochloride Injection

Sponsor: Bedford Laboratories

Product Labeling

Date: January 22, 1998

Proposed labeling changes submitted by the sponsor have been reviewed. The attached recommended revisions to those changes should be communicated to the sponsor.

/S/

Donna Griebel, M.D.
Medical Reviewer

/S/

1/26/98
Julie Beitz, M.D.
Medical Team Leader

cc:

NDA # 50-731

HFD-150/Division File

HFD-150/P. Guinn

HFD-150/D. Griebel

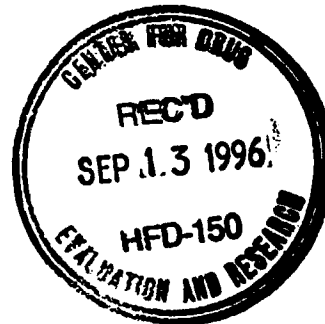


ORIGINAL

ORIG. AMENDMENT
22

September 12, 1996

Division of Oncologic Drug Products
CDER Oncology Group (HFD-150)
Food and Drug Administration
5600 Fisher Lane
Rockville, MD 20857



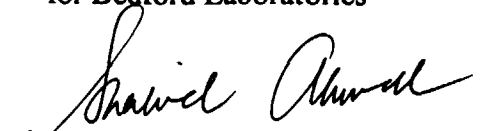
RE: NDA 50-731/Daunorubicin Hydrochloride Injection - 5 mg/mL, 4 mL vial

Dear Sir/Madame,

This is in response to your communication of June 20, 1996, regarding the package insert deficiencies. Attached is a revised draft package insert in which the changes proposed have been highlighted.

We trust this meets with your approval. If you have any questions or comments, please call the undersigned at (216) 232-3320, ext. 218.

Sincerely,
for Bedford Laboratories™


Robert V. Kasubick, Ph.D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

June 21, 1996



ORIGINAL



Dianne Spillman
Project Manager
Division of Oncologic Products
CDER Oncology Group (HFD-150)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 50-731/Daunorubicin Hydrochloride Injection-5mg/mL, 4mL/Vial

NEW CORRESP
(BC/NC)

Dear Dianne:

A response was sent to your attention regarding the EA for Daunorubicin Hydrochloride Injection on June 20, 1996. But the manufacturing facility description was inadvertently not included with the response.

Enclosed herewith is the manufacturing facility description and the pertinent CADD drawings and the letter indicating change of ownership from Cetus Ben Venue Therapeutics to Bedford Laboratories for the Daunorubicin Hydrochloride application.

Please accept my apology for the oversight and I look forward to hearing from you soon.

Sincerely,

A handwritten signature in dark ink, appearing to read "Shahid Ahmed".

Shahid Ahmed
Regulatory Affairs Manager



June 20, 1996

Dianne Spillman
Project Manager
Division of Oncological Drug Products
CDER Oncology Products
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 50-731/ Daunorubicin Hydrochloride Injection 5mg/mL, 4mL vial

Dear Dianne:

Bedford Laboratories has assumed the ownership for the above referenced application on May 2, 1996.

Bedford Laboratories commits to all agreements, promises and conditions previously made by Cetus-Ben Venue Therapeutics, or were contained in the above referenced application. Bedford Laboratories has full copies of the original application and all subsequent submissions.

Bedford Laboratories commits to advising the Agency about any change in the conditions in the above referenced application, as stated in 21 CFR §314.70.

Sincerely,

A handwritten signature in dark ink, appearing to read "R. V. Kasubick", written over a horizontal line.

For R. V. Kasubick, Ph.D.
Vice President Regulatory Affairs

Cetus-Ben Venue Therapeutics

4560 Horton
Emeryville, California 94608
(510) 420-3300

June 20, 1996

Dianne Spillman
Project Manager
Division of Oncologic Drug Products
CDER Oncology Group (HFD-150)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 50-731/ Daunorubicin Hydrochloride Injection, -5mg/mL, 4mL vial

Dear Dianne:

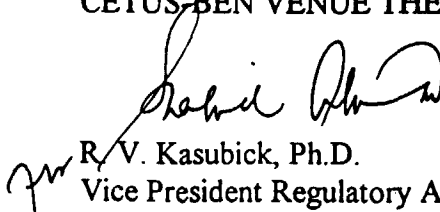
In accordance with 21 CFR §314.72 Cetus-Ben Venue Therapeutics is notifying the Agency that all rights to the above referenced application are transferred to

Bedford Laboratories
Division of Ben Venue laboratories, Inc.
300 Northfield Road
Bedford, OH 44146

This transfer took place on May 2, 1996.

Cetus-Ben Venue Therapeutics has made available to Bedford Laboratories full copies of the original application and all subsequent submissions.

Sincerely,
CETUS-BEN VENUE THERAPEUTICS


R. V. Kasubick, Ph.D.
Vice President Regulatory Affairs

1-1

Cetus-Ben Venue Therapeutics

4560 Horton Street
Emeryville, California 94608
(510) 655-8730

Please direct all correspondence concerning this application to the undersigned at the following address: 300 Northfield Road, Bedford, Ohio, 44146.

December 11, 1995

ORIGINAL

Food and Drug Administration
CDER Oncology
Drug Group HFD-150
1451 Rockville Pike
Rockville, MD 20852
Attn: Dianne Spillman

ORIG ALTIMENT

(BC)

Re: Response to Telephone Request
Product: NDA 50-731/ Daunorubicin Hydrochloride Injection - 5 mg/mL, 4 mL/vial

Dear Ms. Spillman:

As requested in your telephone conversation with Mr. Shahid Ahmed of Ben Venue Laboratories, Inc., we wish to clarify the clinical data in support of the above-referenced New Drug Application.

Please refer to Wyeth's New Drug Application for Cerubidine®, NDA 50-484, for clinical data which applies to Cetus-Ben Venue Therapeutics' NDA 50-731. Daunorubicin Hydrochloride Injection, 5 mg/mL, 4 mL/vial is a solution intended solely for intravenous administration and it contains an active ingredient in the same concentration as the drug product (when reconstituted) which is the subject of an approved New Drug Application (Wyeth's Cerubidine®, NDA 50-484). CBVT does not intend to seek approval for any additional indications than those already approved.

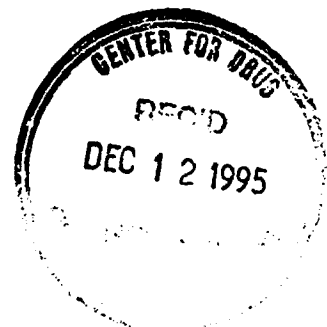
Please also refer to the attached Abbreviated Environmental Assessment, which has been requested by your office.

We trust this meets with your approval. If you have any questions or comments, please call me at (216) 232-3320, ext. 218.

For Cetus-Ben Venue Therapeutics

 RP

Robert V. Kasubick, Ph.D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.



Cetus-Ben Venue Therapeutics certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug product are in conformity with current Good Manufacturing Practices, in accordance with Title 21 CFR 210 and 211. Cetus-Ben Venue Therapeutics' signed statement is provided in Section IX (Manufacturing Facility) Subsection 3 (cGMP Certification).

Three copies of the analytical methods provided in this submission are included in a separate envelope. One copy of the Microbiological Validation, along with the drug products' specifications, stability protocols and the package insert is enclosed separately with this application. This drug product was aseptically filled.

If the Agency has any comments or further requests or if we could be of any assistance in your review, we welcome direct and immediate telephone contact at (216)232-3320, ext. 218.

Sincerely,
for Cetus-Ben Venue Therapeutics

A handwritten signature in black ink, appearing to read "Robert V. Kasubick Ph.D.", written in a cursive style.

Robert V. Kasubick, Ph.D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.